Abstract

Session 4 *Oral Abstract Session*
Antiretroviral Chemotherapy: New Agents
Session Time: Monday, 10 am - 12:30 pm
Room 6A-B

10:00 **1. SCH C: Safety and Antiviral Effects of a CCR5 Receptor Antagonist in HIV-1- Infected Subjects**

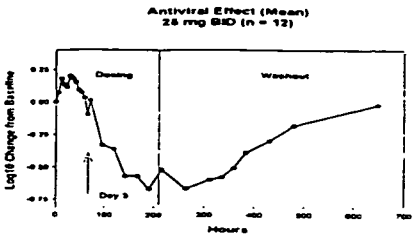
J. Reynes[1], R. Rouzier[2], T. Kanouni[2], V. Baillat[2], B. Baroudy[3], A. Keung[3], C. Hogan[4], M. Markowitz[4], and M. Laughlin[*3]

[1]Univ. Hosp., Montpellier, France; [2]Ctr. CAP, Montpellier, France; [3]Schering Plough Res. Inst., Kenilworth, NJ; and [4]Aaron Diamond AIDS Res. Ctr., Rockefeller Univ., New York, NY

Background: SCH C is an orally bioavailable CCR5 receptor antagonist with potent *in vitro* antiviral activity against a broad selection of primary HIV-1 isolates. The safety and tolerability as well as pharmacokinetic profile have been described in healthy volunteers to doses as high as 600 mg as a single dose (mean Cmax ~2100 nM) and 400 mg/day as multiple (14 days) doses (mean Cmax ~1400 nM). Prolongation of the QTc interval was noted at the 600-mg single dose and at the 400-mg/day multiple dose level. The *in vivo* potential for antiviral effects of SCH C is currently being investigated in an ongoing, sequential rising dose trial (12 subjects/group) as monotherapy with daily doses of 50 mg, 100 mg, and 200 mg in HIV-infected subjects

Methods: 12 adults chronically infected with HIV 1 currently on no antiretroviral agents and with CD4+ cell counts above 250/mm^3 were administered 25 mg SCH C orally every 12 hours for 10 days. HIV-1 RNA levels were determined every 6 hours for 72 hours and then every 24 hours for the remaining 10 days of dosing. In addition, periodic HIV-1 RNA levels were determined during 18 days of follow-up. Subjects had SI/NSI phenotyping prior to dosing, at the end of dosing and at follow-up. Subjects with an SI phenotype at baseline were excluded from participation. The pharmacokinetic profile was determined.

Results: SCH C was safe and well tolerated. Preliminary analysis of the pharmacokinetic profile was similar to healthy volunteers with mean Cmax and Cmin levels at steady state of approximately 140 nM and 90 nM, respectively. The figure shows the antiviral effects of SCH C over the 10 days of dosing and during washout. As shown there is a short lag time in effect as well as a prolonged effect following cessation of dosing. 10 of 12 subjects had at least a 0.5 $\log_{10}$ reduction from baseline during dosing, with 4 subjects achieving 1.0 $\log_{10}$ or greater reduction.



Conclusions: Preliminary data with SCH C supports the CCR5 receptor as a viable target for antiretroviral therapy.